REMARKS/ARGUMENTS

Examiner Westerberg is thanked for courtesies extended to Applicants' undersigned representative during a telephonic interview on February 25, 2010. During that interview, Examiner Westerberg explained that, in her view, deletion of the word "diabetic" from line 2 of claims 10 and 18 broadened the method to encompass treatment of diffuse macular edema that is not necessarily caused by diabetes. That was never the intention of the amendment, so Applicants have added "diabetic" back to line 2 of claims 10 and 18, and have also added "diabetic" to the last phrase of claims 10 and 18 to make this point clear. Since the changes to the claims do not create new issues for Examiner Westerberg to consider, it is respectfully submitted that this Amendment should be entered pursuant to Rule 116.

The following is a reiteration of the entire Remarks section from the first Amendment After Final Rejection filed February 10, 2010, which was not entered.

Claims 10-12, 14, 18, 20 and 21 are pending herein. Independent claims 10 and 18 have been amended to overcome formal rejections and claim 19 has been cancelled to advance prosecution. The claims have been further amended also to be more specific regarding the nature of the affliction being treated; the claims now recite in the preambles that "diabetic macular edema" is being treated and the human subject to which the active ingredient is administered is one "having diffuse macular edema."

The Examiner stated that use of different terms weakened Applicants' position in support of patentability here. Applicants point out that diabetic maculopathy is the name of a disorder, while diabetic macular edema is a pathological condition of diabetic maculopathy in Japan. As treatment of diabetic macular edema leads to treatment of diabetic maculopathy, diabetic maculopathy and diabetic macular edema are often used together. There is no problem or inconsistency in the terminology. But in the USA, "diabetic macular edema" is used as the name of a disorder which is independent from diabetic maculopathy, as stated by Dr. Lorenzi in the Rule 132 Declaration filed herewith. The claims have been amended to follow the use of these terms in the USA.

That is, the claims specify treating "diabetic macular edema." This amendment will make the point more clear.

Moreover, the phrase "a human subject having" has been added to the preamble of claim 14 to be consistent with claim 10. The addition of this phrase helps clarify the claim.

No new issue has been added in these amended claims.

In addition, the terms are supported in at least the following portions of the substitute specification: the paragraph bridging pages 1 and 2 (see the second sentence), page 2, first full paragraph (see the first sentence), page 4, first full paragraph (see the last sentence), page 5, second sentence, page 6, first paragraph, the paragraph bridging pages 8 and 9, and the working examples including the clinical trial results; see the first sentence in the paragraph bridging pages 15 and 16 referring to "ten patients with diabetic macular edema."

The present invention is directed to the discovery that a particular type of compound indicated by the formula in independent claims 10 and 18 is effective in treating humans having diffuse macular edema. The references used to reject the claims do not teach or suggest such a treatment. Arguments in support of Applicants' position will be presented below.

Enclosed is a further Rule 132 Declaration of Dr. Mara Lorenzi, whose Declaration was filed with the last reply. Here, Dr. Lorenzi discusses at pages 9 and 10 that the concerns of the Examiners regarding inconsistencies of terminology are unnecessary and that the focus remained "on one basic entity," namely diabetic macular edema, a term used in the pending claims. Dr. Lorenzi explains that diffuse macular edema refers to the sites of leakage and explains in detail the difference between diffuse and focal leakage. Dr. Lorenzi also discusses maculopathy and concludes that "[b]ecause maculopathy may at some point no longer be reversible, the condition of interest from the standpoint of interventions is diabetic macular edema. The earliest the intervention, the better the chances of resolution." Dr. Lorenzi also points out that the

definition used is that of the diabetes and ophthalmology communities in the USA. The revised claims are intended to make this understanding clear.

1. Claims 10 and 18 were objected to for not making "sense" because the last active step of each of the criticized claims was followed by the chemical formula. Claims 10 and 18 have been amended to place the steps following the first active step in the claim at the end and beyond the chemical formula. (And, as noted above, the disease being treated as "diabetic macular edema" and the human subject is one "having diffuse macular edema.") Should the Examiner believe that further changes are required in these claims, she is asked to contact the undersigned.

2. Claim 19 was rejected under §112, second paragraph, as indefinite. The claim has been cancelled to advance prosecution.

3. Claims 10-12, 14 and 18-21 were rejected under §102(b)/103(a) over Mylari. This rejection is respectfully traversed.

The Examiner asserts in the most recent Office Action that the art, not used to reject claims, but addressed in Dr. Lorenzi's Declaration filed June 29, 2009 shows that patients with diabetic retinopathy (DR) may develop diabetic maculopathy (DM) or, more particularly, diabetic macular edema. The Examiner thus asserts that the art shows a "nexus" between the diseases and that, therefore, Mylari teaches or suggests the claimed invention. Applicants respectfully disagree.

In the first instance, it has been established earlier in the prosecution that the use of a compound such as SNK-860 in the clinical treatment of DR has been shown to have no effect. See, for example, the paragraph bridging pages 9 and 10 of the Amendment filed July 16, 2008. Therefore, one of ordinary skill in the art would not expect to use such a compound in the clinical treatment of diabetic macular edema.

The "nexus" mentioned by the Examiner occurs in no reference that deals with the treatment of DR and diabetic macular edema. The last sentence in the Abstract and the specification at Column 1, lines 57-59 in Mylari, while mentioning DR, do not mention diabetic macular edema. Moreover, the working examples in the reference are

formulation examples and there is no indication of actual clinical treatment using the composition containing an ARI disclosed in that reference.

In addition, although patients with diabetic retinopathy in Mylari may have diabetic macular edema, it is but a statistical possibility and is not a fact disclosed in the reference. As noted above, no reference mentioning both DR and diabetic macular edema discusses treating both with the same active ingredient. The record is replete with discussions of how DR and diabetic macular edema are deemed separate afflictions. Taking the Examiner's position to extremes, prior art that discloses the administration of SNK-860 to a human anticipates every invention regarding the administration of SNK-860 for treatment of a disorder because a portion of humans (X% of all humans) statistically have such a disorder. Using this way of thinking, an invention related to the administration of a medicament for treatment of a disorder is made when there is a statistical possibility that the patients have that disorder, but a statistical possibility does not constitute an invention; a confirmed effect of the administration of the medicament to patients with such a disorder is necessary in order to complete same.

As explained previously, while diabetic macular edema is a complication of DR, diabetic macular edema is a disease different from DR as explained by Dr. Lorenzi at pages 9 and 10 of her Declaration. Diabetic complications are diseases different from diabetes. The rejection should be withdrawn.

4. Claims 10-12, 14 and 18-21 were rejected under §103(a) over Akita in view of Wani. This rejection is respectfully traversed.

As in the previous rejection, the primary reference discusses DR, but not diabetic macular edema, here the treatment of diabetes-induced rat models with an ARI, particularly SNK-860. The secondary reference, which discusses patients having both DR and diabetic macular edema, does not talk about treatment using the same active ingredient and, as in the prior rejection, there is nothing in the references themselves that show or suggest that the treatment of DR with a particular material or compound leads one of ordinary skill in the art to a belief or conclusion that the same material or

composition can and should be used in the treatment of diabetic macular edema. The record in the case establishes the unexpected nature of the invention (see the discussion in the Declaration of Mr. Kato filed July 16, 2008) and explains that diabetic macular edema is a disease different and independent from DR, calling for different methods of treatment (see page 9 in the Declaration of Dr. Lorenzi filed June 29, 2009) and different end points. This situation is similar to the case where a diabetic complication is a disease different and independent from diabetic mellitus. The claims patentably define over the art because the claims are directed to a method, as explained in the record to date, that is neither suggested by nor apparent from the references of record.

The art is summarized in the context of the record thusly. Diabetic macular edema and DR are diseases different and independent from each other, having different methods of treatment and end points. Moreover, as described in the literature, in the treatment of diabetic macular edema, treating diffuse macular edema is important, although difficult to treat. Furthermore, the treatment of diffuse macular edema differs from the treatment of focal macular edema. Akita discloses the effectiveness of SNK-860 to focal retinal edema in a rat model. Such a teaching does not lead one to an expectation of success in treating diffuse macular edema. Mylari discloses the administration of SNK-860 to patients with diabetic retinopathy. However, the compound had no effectiveness in clinical trials of diabetic retinopathy. (Yet, as the present case shows, the compound showed explicit effects in clinical trials of diabetic macular edema, clearly an unpredictable effect.) Lopes de Faria discloses the importance and difficulty of the treatment of diffuse macular edema. Pedro Romero Aroca discloses the importance of the distinction between diffuse and focal macular edema in the treatment. Speicher discloses ARI has a good effect on animals but it does not have an effect on humans. Wani states that diabetic maculopathy is related to diabetic retinopathy and these two diseases are overlapping each other. One of ordinary skill in the art knows that therapies of diabetic retinopathy and diabetic macular edema are different from each other and the fact is disclosed, for example, in Mohamed.

Furthermore, the only ARI that showed effectiveness of diabetic retinopathy clinical trials was epalrestat, reported long ago in 1990. Clinical trials for diabetic retinopathy were also undertaken with sorbinil, an ARI with a chemical structure similar to SNK-860, without success. No clinical trials were reported in the literature of using an ARI to treat diabetic macular edema. The unpredictable and prominent pharmological effects of SNK-860 in the treatment of diabetic macular edema are shown in the clinical data of patients with diabetic macular edema in the specification and the experimental data of a monkey model reported in the Declaration of Mr. Kato filed July 16, 2008. That Declaration showed also that epalrestat, an ARI effective in clinical trials of diabetic retinopathy, was not effective in the monkey model. The present invention shows for the first time a treatment effective in clinical trials for diabetic macular edema. The art does not lead a person skilled in the art to the claimed invention.

If Examiner Westerberg believes that further contact with Applicants' attorney would be advantageous toward the disposition of this case, she is herein requested to call Applicants' attorney at the phone number noted below.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 50-1446.

Respectfully submitted,

February 26, 2010
Date

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SPB/CW/tlp

Attachment:
Rule 132 Declaration of Dr. Mara Lorenzi (10 pages)

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